Title
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ISBN
9780120884889

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Publication Date
2008-12-01

DOI
10.1016/B978-012088488-9.50053-X

CHAPTER 50

The Effects of Electrolyte Disorders on Excitable Membranes

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THE NATURE OF EXCITABILITY

In 1902, Julius Bernstein (9) hypothesized that cells were bounded by membranes selectively permeable to K^+ ions at rest and permeable to other ions when excited. Over the past 50 years, we have learned this hypothesis to be correct in its essentials, and the agents of such permeation are transmembrane proteins called ion channels (51). Ion channels are present in all membranes. They underlie minute biological events such as the response of a single rod cell to a photon of light, degranulation of an activated mast cell, and proliferation of a T cell in response to a specific antigen. Ion channels also mediate spectacular events like heart beats, fluid and electrolyte homeostasis, intestinal peristalsis, and memories. Today, identification of genes for ion channels and their regulatory subunits has been combined with sensitive methods that allow characterization of channel function at remarkable resolution; the behavior of single molecules can be evaluated in real time. In this chapter, we will discuss the key elements of how ion channels participate in maintaining the cellular membrane potential as well as how excitable cells are activated. We also present advances in our understanding of ion channel structure and modulation of ion channel activity. In terms of these fundamental principles, we will explain how electrolyte disturbances can lead to serious dysfunction of nerve, muscle, and the heart.

Selective Permeability, Membrane Potentials, and Ionic Gradients

Electrical signals are the fastest means of communication in the body. The flow of electricity provides a rapid way for the dendritic tree of a neuron to integrate inputs from a finger placed on a hot stove, initiate reflex withdrawal of the painful appendage, inform the brain of the developing situation, and coordinate synchronized contraction of the heart in the finger's startled owner. In clinical settings, these events can be monitored by extracellular recordings such as electrocardiograms (ECGs), electroencephalograms (EEGs) and electromyograms (EMGs), which measure small signals (typically microvolts) due to electric currents that are generated by excitable cells. Such signals are a distant reflection of what is happening at the cell membrane where neurotransmitter release, contraction, and excitability itself are unfolding. To understand excitability (and how it gives rise to the extracellular signals our clinical tools detect) we must consider what is learned from intracellular recordings.

A microelectrode is a glass tube (usually ~1 mm wide with a tip drawn down to ~0.5 μm) that is used to penetrate a cell membrane with minimal damage so the membrane can reseal tightly around the glass. Consider two such electrodes in a salt solution bathing a cell (Fig. 1A). The electrodes are filled with a conducting solution (e.g., 150 mM KCl) and connected through a voltmeter by a silver wire that serves to establish electric continuity between the solutions. The voltmeter reads zero since the system is at equilibrium. If one of the electrodes is advanced across a cell membrane into a living cell, the voltmeter registers an abrupt change revealing an electrical potential difference between the two electrodes; this is the membrane potential (Fig. 1B), which is set up by the motions of ions across the membrane and represents a balance of chemical and electrical forces. How this develops is most readily understood if we first consider just the major cations (K^+ and Na^+) and anion (Cl^-) in cells and serum.

Active transport systems, such as the Na^+-K^+ pump, keep cytosolic K^+ levels high and Na^+ levels low (Table 1). Pumps are slow (maximal turnover rates of 60–100 Na^+ ions each second), but are present in cells at high abundance (10^5–10^7 per cell) and serve to couple the use of cellular energy (hydrolysis of adenosine triphosphate [ATP]) to each transport event. This establishes an ionic gradient across the membrane which serves as a reservoir of chemical energy due to the decreased entropy. The cell is now poised to use this stored energy by opening ion channel pathways through the membrane. Ion channels are fast (transporting 10^6–10^8 ions each second), low-abundance proteins (10–1000 per cell) that dissipate ionic gradients by opening a water-filled pathway across the membrane to allow free diffusion of selected

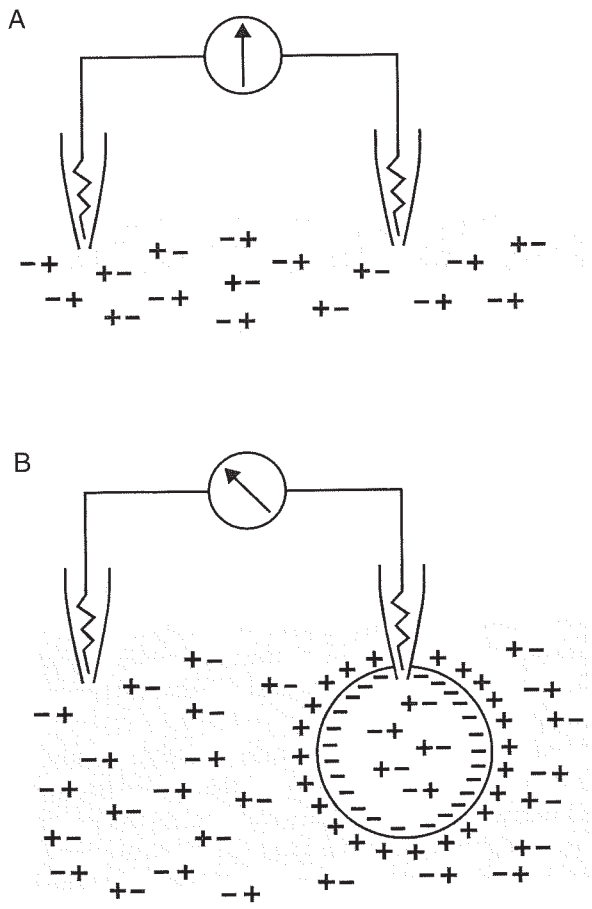

FIGURE 1 Schematic representation of a voltmeter and mammalian cell in serum. **A:** The voltmeter measures no potential difference when both electrodes are outside the cell in the bath solution. **B:** The voltmeter registers a negative membrane potential when one electrode moves into the cell. Excess negative charge inside the cell at equilibrium represents a small fraction of the total number of charged ions in the cell. The unbalanced charges accumulate at the membrane.

ions down their electrochemical gradients. Thus, an open K^+ channel allows K^+ ions to diffuse out of a cell down the K^+ concentration gradient, leaving behind negative counterions. The excess of negative charge inside the cell constitutes an electrical energy that is registered on the voltmeter as a negative membrane potential (Fig. 1B). Although this electrical energy can be large, the imbalance of charge reflects a miniscule fraction of the total number of ions within the cell (see next section).

If the channel stays open, K^+ ions continue to flow until the chemical energy favoring outward K^+ movement (down the concentration gradient) is balanced by the electrical energy favoring movement of the positively charged ions into the negative cell interior (down the electrical gradient). At equilibrium, the forces are equal, efflux equals influx, and there is no net movement of K^+ ions across the membrane. The Nernst potential is the membrane potential that yields equilibrium for transport of a particular ionic species across a membrane (and is one of two key relationships central to cellular electrophysiology). For a purely K^+ selective membrane, the Nernst potential is the same as the equilibrium potential for K^+ ions, E_K, and is expressed as:

TABLE 1 Typical Ionic Composition of Muscle Cells and Serum and Equilibrium Potential

Ion (X)	Cell (mM)	Serum (mM)	$E_{rev} = \frac{RT}{zF} \ln \frac{[X]ext}{[X]in}$
Sodium (Na^+)	12	145	+67
Potassium (K^+)	155	4	−97
Chloride (Cl^-)	4	125	−93
Calcium (Ca^{2+})	<0.0001	1.5	>100
Magnesium (Mg^{2+})	1–15	1	–

Source: Hille B. *Ion Channels of Excitable Membranes*, 3rd ed. Sunderland, MA: Sinauer; 2001; and Dyckner T, Wester PO. The relation between extra- and intracellular electrolytes in patients with hypokalemia and/or diuretic treatment. *Acta Med Scand* 1978;204:269–282.

$$E_K = \frac{RT}{zF} \ln \frac{K_{ext}}{K_{in}} \qquad \text{(Eq. 1)}$$

where R is the gas constant, T is the temperature in degrees Kelvin, z is the charge of the ion, F is the Faraday constant, and K_{ext} and K_{in} the concentrations of K^+ in the extracellular and intracellular compartments, respectively. For K^+ ions at physiological temperature (37°C), RT/zF is ~27 mV and E_K is, ~ −97 mV. The Nernst potentials of Na^+, K^+, Cl^-, and Ca^{2+} for a typical cell in serum are given in Table 1. Mammalian cells have resting potentials of −60 to −90 mV because K^+ ions are not the only ions that cross cell membranes at rest. Thus, pathways for transmembrane Na^+ flux allow these ions to flow down their chemical and electrical gradients into the cell and shift the membrane potential toward the Nernst potential for Na^+ ($E_{Na} \approx +67$ mV). The resting membrane potential of a cell (E_m) results from the permeability and concentration gradients of all ions in the system. Resting potentials are close to E_K because more K^+ selective pathways are open in resting cells than those for other ions.

Definitions, Nomenclature, and Why Electrical Signals Are So Fast

A brief foray into the units and measures of excitation is needed to make the biology of excitation accessible. Net flow of charge is called current (abbreviated, I). Conductance (G) is a measure of the ease with which current flows between two points. The potential difference (ΔV) is defined as the work required to move a unit of charge from one point to another. These three measures are related by the second key relationship of cellular electrophysiology, Ohm's law:

$$I = G\Delta V \qquad \text{(Eq. 2)}$$

This equation indicates that the current (measured in amperes, A) is equal to the product of the conductance (measured in siemens, S) and the potential difference across the

conductor (measured in volts, V); by convention, positive current flows in the direction of movement of positive charges. Ohm's law can also be written in terms of resistance (R) to current flow (measured in ohms):

$$R = \frac{I}{\Delta V} \qquad \text{(Eq. 3)}$$

When 1 V is applied across a 1-ohm resistor or a 1-S conductor, a current of 1 A flows. Ion channels in the cell membrane act as conductors that span an insulator. When an insulator is interposed between two conducting solutions, it acts as a capacitor. The capacitance (C, measured in farads, F) of the insulator arises from the attraction of separated charges across the barrier and depends on its geometry and dielectric constant (ε). The specific capacitance of human cell membranes is ~1 μF/cm^2 and is a measure of how much charge (Q) must be moved from one side to the other to set up a given potential difference:

$$C = \frac{Q}{\Delta V} \qquad \text{(Eq. 4)}$$

It is now possible to understand why electrical signals are so rapid. Reconsider the small cell in Fig. 1 with a diameter of 12 μm and a resting membrane potential of −100 mV. This cell has a capacitance of 10^{-11} F and, therefore, 6 million positive charges left the cell (Eq. 4) to produce the resting potential. While this sounds significant, it represents less than 1/10,000 of the total cations in the cell (a volume of 10^{-12} L with 150 mM cations indicates 10^{11} total cations before the exodus). Figure 1B emphasizes two salient features. First, almost all ions in the cell and the external solution have balancing counter-ions; in contrast, unbalanced charges are at the membrane boundary. This is because unbalanced charges repel each other and move apart until their movement is limited. Second, unbalanced charges at the membrane are not necessarily the same as those produced initially by charge separation. Because ions are always in motion, they often exchange places. Thus, an unbalanced ion in the center of the cell will repel its neighbors, causing them to repel their neighbors, and so on until the unbalanced charge resides at the bounding membrane surface. This process (which is simply the conduction of electricity in an ionic solution) is much faster than diffusion. That is, it would take much longer for the original ion to diffuse to the membrane than it actually takes for its electrical influence to be felt. This is the fundamental mechanism that makes electrical signals fast.

By convention, the current across a membrane is taken as positive when positive charges are moving outward. Current is equal to the change in charge over time, $dQ/dt = I$. Combining this with Eq. 4 gives the relationship between changes in membrane voltage and time, assuming the capacitance change is negligible:

$$\frac{d\Delta V}{dt} = -\frac{I}{C} \qquad \text{(Eq. 5)}$$

The effect of opening one channel with a typical current of 1 pA (6×10^6 charges/sec) in our 12-μm cell is to cause the membrane voltage to change at a rate of −100 mV each second (6×10^6 charges/sec divided by 6×10^7 charges/V). As K^+ ions are moving toward their equilibrium condition, the voltage is shifting toward E_K. If two channels were to open at once, the membrane potential would change at twice the rate.

Voltage-Clamp Technique and Ionic Currents

Much of what we understand about electrical signals comes from application of voltage-clamp technique. Developed by Cole and Marmont in the 1940s, it was applied shortly thereafter to studies of the ionic basis for action potentials, notably by Hodgkin and Huxley (53–55). In voltage-clamp technique, the membrane voltage is controlled by the experimentalist and the current that flows to maintain the commanded voltage is measured. It is common to make voltage-clamp measurements on a small patch of membrane isolated on the tip of a glass pipette with a high-resistance (gigaohm) seal (Fig. 2). In on-cell

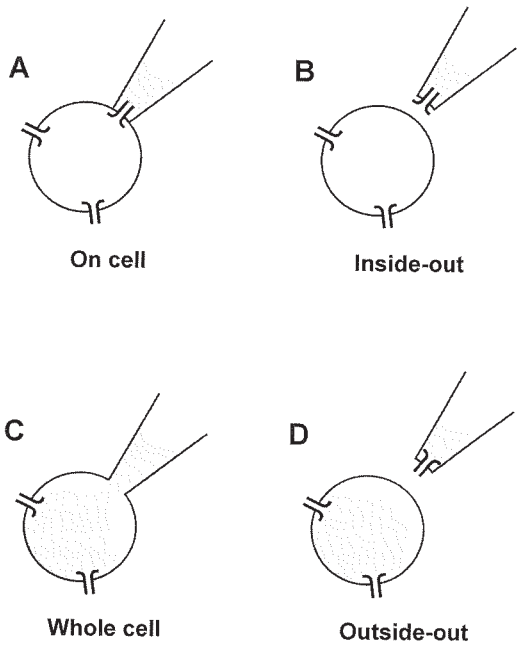

FIGURE 2 Schematic representation of the modes of voltage-clamp analyses. First, a high-resistance seal is formed between the electrode glass and the cell membrane (on-cell mode, **A**); the membrane patch can then be pulled off the cell, exposing its cytoplasmic face to the bath solution (inside-out mode, **B**). Alternatively, the on-cell seal can be broken so that the pipette solution is in free communication with the cell interior (whole-cell mode, **C**); from whole-cell mode, the pipette can be withdrawn to form an excised membrane patch with the extracellular membrane face exposed to the bath (outside-out mode, **D**). (For methodologic detail, see Kettenmann H, Grantyn R. *Practical Electrophysiological Methods*. New York: Wiley-Liss; 1992:249–299.)

mode, channels in the patch maintain continuity with the intracellular contents (and thus regulatory influences). The patch can be excised from the cell in inside-out or outside-out configuration allowing the experimentalist to control solution composition on both sides of the membrane. If the cell-attached patch is broken while the pipette maintains tight contact with the cell membrane, the voltage of the entire cell can be controlled and whole-cell currents from the composite activity of all channels in the cell are measured.

The recorded activity of a single K^+-selective ion channel in an on-cell membrane patch is shown in Fig. 3. The opening of this one channel allows 5×10^7 K^+ ions to cross the membrane each second when the membrane is clamped to −120 mV. Channels are characterized by their single-channel conductance (γ, measured in picosiemens, pS) and unitary current (i, measured in picoamperes, pA) as distinguished from G and I, the conductance and current of a population of channels. Graphing the single-channel current amplitude against membrane voltage gives a current-voltage relation or i-V curve (Fig. 3). Applying Ohm's law (Eq. 3) to the single-channel data ($\gamma = i/\Delta V$) shows that the slope of the i-V relation is the single-channel conductance and the intercept with the voltage axis is the reversal potential at which no current flows. The reversal potential for the channel in Fig. 3 is close to E_K determined by the Nernst relation (Eq. 1), as expected for a K^+ channel.

Sodium and Potassium Channels and Action Potentials

Voltage-gated channels open (activate) in response to changes in membrane potential because the electric field acts on the channel to change its protein conformation (or state). It is voltage-gated sodium (Na^+) channels that initiate action potentials and voltage-gated K^+ channels that cause them to end. Action potentials are large depolarizations (positive movements) of membrane potential associated with neural signals and muscular contraction (Fig. 4). In excitable cells, basal efflux of K^+ ions keeps the cell potential at negative (or polarized) values near E_K. An initial depolarization causes Na^+ channels to open, allowing positive Na^+ ions to flow into the cell down their concentration gradient and shifting the membrane potential in the positive direction. At some potential, Na^+ influx is greater than K^+ efflux and net current is inward. At this threshold, the membrane begins to move regeneratively to positive potentials as more and more Na^+ channels open and the membrane potential rushes toward E_{Na}. The threshold is set by a balance of K^+ and Na^+ channel activity and is thus controlled by regulation of channel gene expression, protein turnover rates, and modulation of channel activity by accessory molecules and second messengers.

The explosive phase of the action potential slows first because voltage-gated Na^+ channels close after opening (in

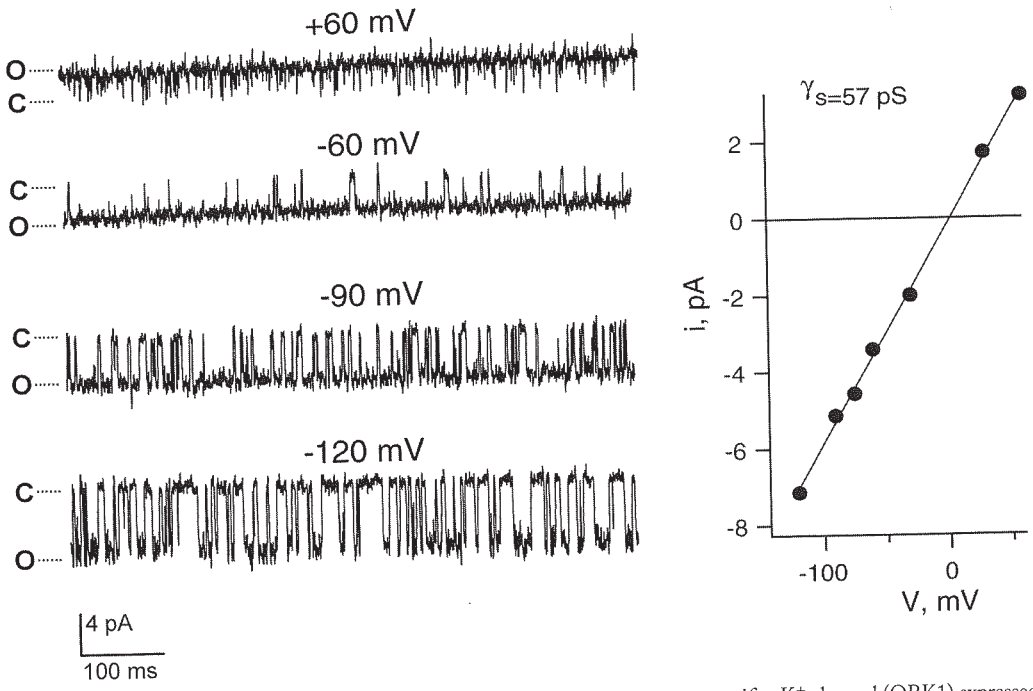

FIGURE 3 Single-channel currents through the *Drosophila melanogaster* open-rectifier K^+ channel (ORK1) expressed in *Xenopus laevis* oocytes and studied in an on-cell membrane patch. The channel has an open probability close to 1.0 during bursts and is shown here in the presence of a blocker, Ba^{2+} (5 mM), to reveal the open (O) and closed (C) state levels (filtered at 1 kHz). The plot shows a unitary slope conductance (γ_s) of 57 pS under these conditions: pipette solution has 140 mM KCl so that E_K is ≈ 0 mV. (From Goldstein SA, Wang KW, Ilan N, et al. Sequence and function of the two P domain potassium channels: implications of an emerging superfamily. *J Mol Med* 1998;76:13–20, with permission.)

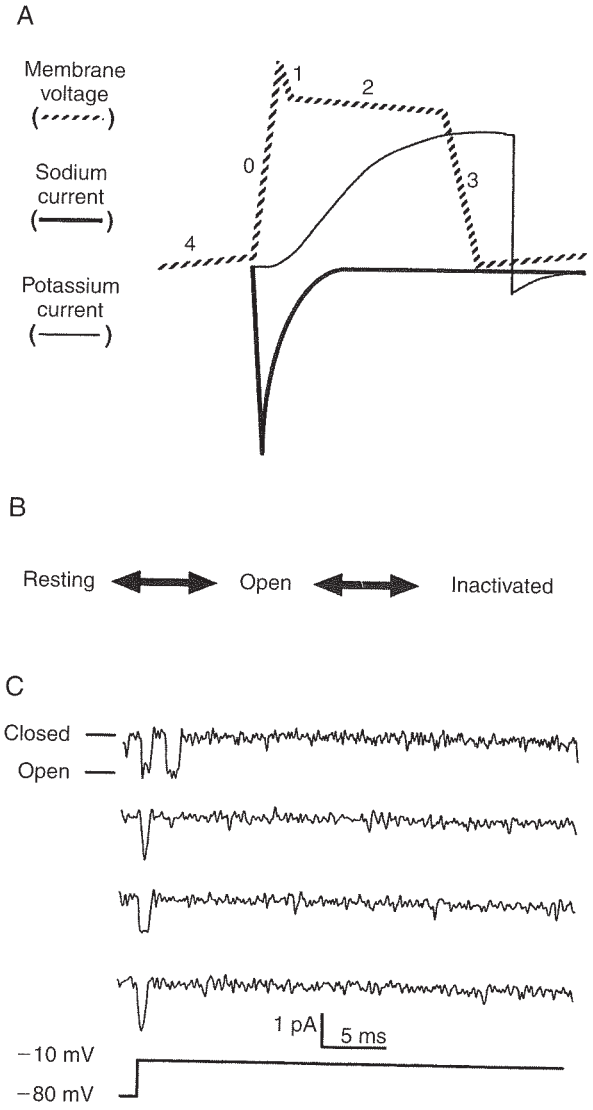

FIGURE 4 Representation of a cardiac action potential with Na^+ and K^+ currents. **A:** Diagram of the phases of a cardiac Purkinje cell action potential with currents through two contributing channels superimposed. (From Fozzard H. *Ion Channels in the Cardiovascular System: Function and Dysfunction.* Armonk, NY: Futura Publishing; 1994:81–99, with permission.) Channel currents associated with the five phases of the action potential: phase 0, rapid depolarization (I_{Na}, I_{Ca}); phase 1, fast repolarization (I_{to}); phase 2, plateau (I_{Ca}); phase 3, delayed repolarization (I_{Kr}, I_{Ks}); and phase 4, pacemaker depolarization (I_{IR}, I_f). **B:** Scheme for gating of an inactivating voltage-gated channel. **C:** Single-channel recordings from a cardiac voltage-gated Na^+ channel. In response to a change in voltage from −80 mV to −10 mV, the channel moves from resting to open conformation and then to an inactive state.

a process called inactivation) despite maintained depolarization (Figs. 4B and 4C). The membrane repolarizes to its negative resting potential when K^+ channels open after a delay; the delay prevents overlap of repolarizing K^+ currents and the initial depolarizing phase of the action potential. Thus, inward Na^+ currents move the membrane potential positively toward E_{Na}, whereas subsequent outward K^+ currents return the cell to rest near E_K. Because it takes some milliseconds for Na^+ channels to recover from inactivation, time during which they do not pass current, the membrane is temporarily inexcitable. This interval is called the refractory period.

The initial movement to threshold comes either from another part of the cell or results from activity of other ion channels. For example, acetylcholine released from a motor nerve crosses the neuromuscular junction to bind to nicotinic acetylcholine receptor channels on the postsynaptic membrane; these channels produce inward cation currents that depolarize the muscle membrane to threshold, initiating an action potential and muscular contraction.

ION CHANNELS

The Ion Conduction Pathway

Before the structure of any integral membrane protein had been determined, ion channels were known to pass ions by forming water-filled holes across cell membranes. First suggested by Hodgkin and Keynes (55) in 1955 and elegantly rendered by Miller (94) in 1987, the porelike structure of ion channels can be divined from four basic attributes. The first we have already considered—high unitary transport rates. Single-channel currents are enormous compared with the turnover rates of other transport proteins. This difference in speed is based on their disparate mechanisms. Non-channel transport events involve the physical movement of the protein with each turnover event. Every translocation requires exposure of a binding site on one side of a membrane, binding of the permeant species, occlusion of the site, a conformational change to allow exposure of the ion on the opposite side of the membrane, and, finally, ion release. Each step must then be carried out in reverse to achieve a complete transport cycle. It is easy to imagine that less time and energy would be spent if opening a passageway permitted diffusion of millions of ions without the need for further conformation changes. The fastest transporters are three orders of magnitude slower than ion channels; the Cl^-/HCO_3^- exchanger, band 3, moves 10^4 chloride ions per second at room temperature.

The second attribute of ion channels that demands a pore structure is their low temperature coefficient for function. The influence of temperature on Na^+ and K^+ currents in the squid axon was studied by Hodgkin, Huxley, and Katz (53) and found to be small ($Q_{10} \approx 1.3$, corresponding to an enthalpic energy barrier of ~5 kcal/mol). This was indistinguishable from the value determined for unrestricted diffusion of the ions in aqueous solution. Since increasing the temperature provides thermal energy to drive protein movements, a low Q_{10} argues against the coupling of any large conformational changes in protein structure to individual ion transport events. Enzymes and carrier-type transporters show a significantly higher enthalpic barrier ($Q_{10} \approx 3$, corresponding to ~18 kcal/mol).

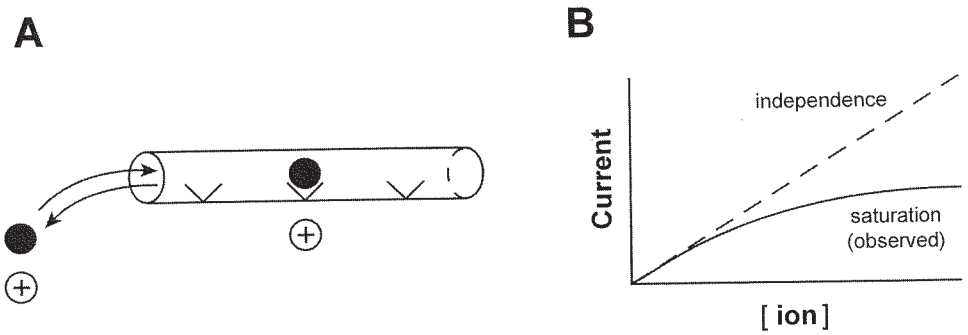

FIGURE 5 **A:** Model of a multi-ion pore. Ions entering a channel may find it occupied and be unable to traverse the membrane. For this reason, ions do not move through multi-ion channels independently but show saturating velocity **(B)** at high substrate concentration. (See Hille B. *Ion Channels of Excitable Membranes*, 3rd ed. Sunderland, MA: Sinauer; 2001; and Hodgkin AL, Keynes RD. The potassium permeability of a giant nerve fibre. *J Physiol* 1955;128:61–88.)

A third attribute of channel function that supports a pore structure is ion–ion flux coupling. Ions crossing the membrane through channels do not act independently. That is, ion flux is not directly proportional to ion concentration because sometimes an ion enters the channel only to find it is occupied and impassable (Fig. 5A). Whether by repulsion between charged ions or mechanical obstruction, increasing ion concentration leads to current saturation (Fig. 5B) just as an enzyme reaches a saturating velocity at high substrate concentration (V_{max} in the Michaelis-Menten model of enzyme kinetics). Ion–ion flux coupling occurs when one ion sweeps another with it through the channel. Experimentally, this is assessed by studying how voltage alters inward and outward ion flux. In squid axons, K^+ ions behave as if they carry a charge of +2 or +3 because they traverse the membrane with one or two other K^+ ions (8, 55).

The fourth phenomenon that argues for a pore structure is ion–water flux coupling. Ion channels contain water in addition to ions. The pore is too narrow to allow the water molecules to pass each other or the ions. This means that if water is forced to flow by hydrostatic or osmotic pressure, it will drag ions across the membrane even if there is no chemical or electrical gradient acting on the ions. A voltage can be applied to reduce the ion current to zero and the value of this voltage (the "streaming potential") can be used to determine the number of water molecules lined up in single file within the pore (93, 109).

High unitary transport rates, low temperature coefficients, ion–ion flux coupling, and ion–water flux coupling are observed in ion channels. These four behaviors have also been demonstrated for gramicidin A, a small-peptide antibiotic known to form a pore in membranes (34). Using x-ray crystallography of ion channels, MacKinnon and colleagues have solved atomic-resolution structures of ion channels, directly showing their pores to be transmembrane pathways filled with water and conducting ions (28, 62, 63, 75). Similar pore structures for voltage-gated Na and ligand-gated channels have been supported by electron microscopy (95, 112).

Ion Permeation: How Channels Are Fast and Specific

In biology, high specificity is typically associated with tight binding as exemplified by antigen-antibody interactions. However, K^+ channels show high specificity (greater than 1000:1 for K^+ over Na^+) and high throughput (10^7 K^+ ions per second) (136). How this is thought to transpire can be understood by considering the structure of the *Streptomyces lividans* K^+ channel, KcsA (Fig. 6). To move across the membrane, K^+ ions must exchange a shell of stabilizing water molecules for new interactions with the channel protein. Na^+ ions do not readily occupy a K^+ pore site as they bind their hydrating waters more tightly, and are too large to enter the pore while hydrated. When dehydrated, Na^+ ions are ≈0.4 Å smaller than K^+ ions so that channel residues optimally positioned to coordinate K^+ appear to be too distant to stabilize a naked Na^+ ion. High-resolution structures (96, 141) of the KcsA channel reveal that two dehydrated K^+ ions are held within the pore by 16 hydrogen bonds that make up the selectivity sequence. The entry of a third K^+ ion to one side of the pore apparently destabilizes the coordination of the resident K^+ ions and causes a repositioning of hydrogen bonding such that the K^+ ion at the opposite side leaves the pore. The three-ion configuration is assumed to be a high-energy transitional state. It is not observed experimentally, but is presumed to underlie the remarkably high throughput of ion conduction in a K^+ channel. A similar mechanism is likely to also operate in Ca^{2+} and Na^+ channels (16, 18).

Channel Proteins and Domain Function: P Loops, Voltage Sensors, and Gates

Ion channels are named for the ions they permit to traverse the membrane. Cloning of genes for voltage-gated Na^+, Ca^{2+}, and K^+ channels made clear their membership in an extended molecular superfamily marked by similarities in primary sequence and predicted membrane topology (60).

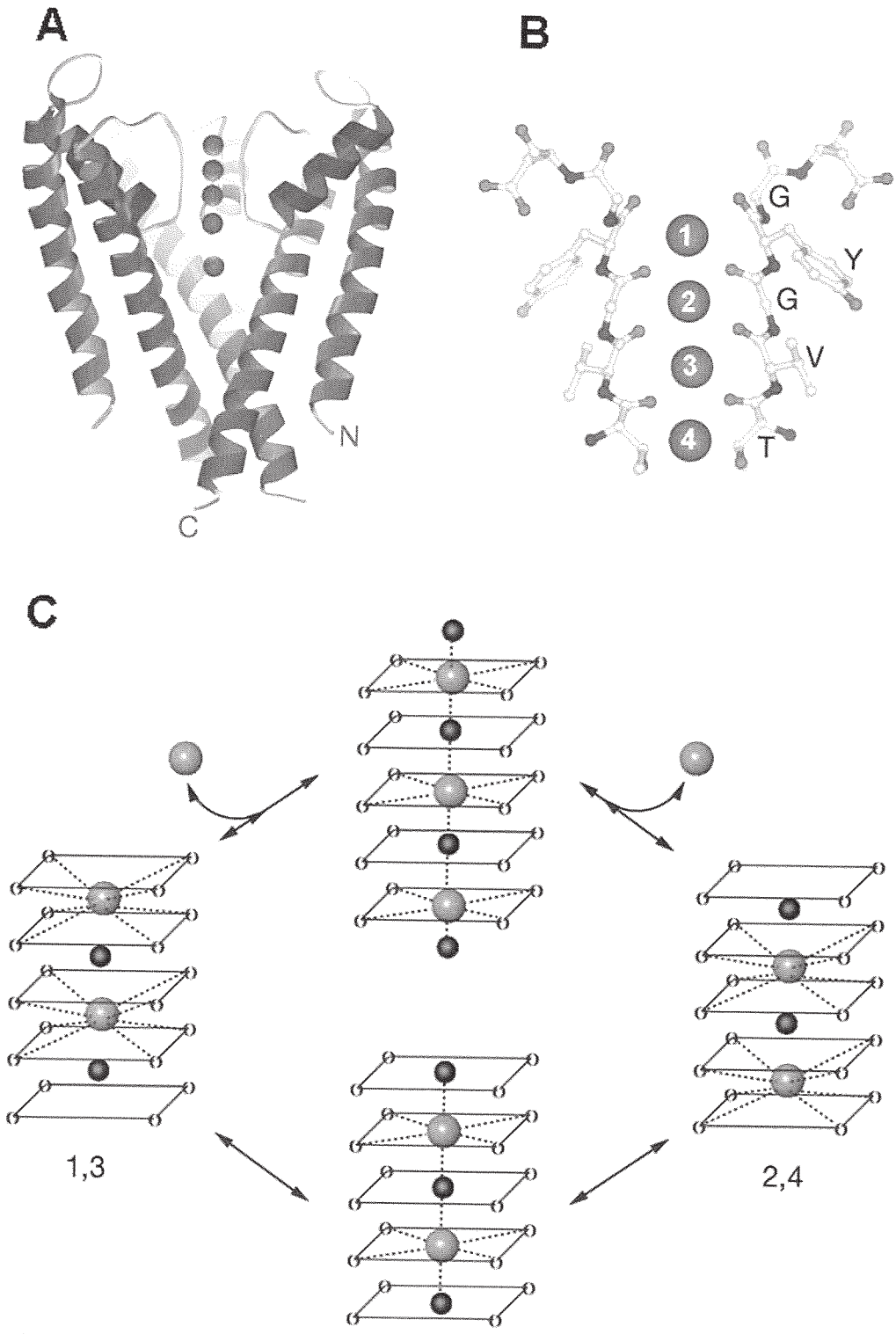

FIGURE 6 Crystal structure of the KcsA K^+ channel. The channel, cloned from *Streptomyces lividans*, was analyzed by x-ray crystallography to a resolution of 2.0 Å. Images reveal four identical subunits forming a transmembrane pore filled with K^+ ions and water molecules. **A:** A ribbon representation of the KcsA channel tetramer viewed from a side view, with the subunit closest to the viewer removed. The selectivity filter is shown as thinner rods and the locations of K^+ binding are seen as spheres. **B:** A close-up view of the selectivity filter, using a ball-and-stick representation, with front and back subunits removed. This narrow region is 12 Å long and lined by main-chain carbonyl oxygen atoms; the K^+ binding sites are numbered, with position 1 closest to the extracellular face. **C:** A schematic of the throughput cycle of K^+ ions through the channel's pore, with K^+ ions and water molecules shown as large and small spheres, respectively. Dotted lines represent hydrogen bonds, and the binding configurations noted as 1,3 and 2,4 are considered to be relatively stable, low-energy states (3 o'clock and 9 o'clock positions). Ion throughput occurs as a new K^+ ion is partially dehydrated and stabilized by hydrogen bonds within the selectivity filter (12 o'clock position). Because this transition is a high-energy state, one of the two peripheral K^+ ions quickly exits the pore. The 6 o'clock position shows an alternative transitional state allowing a switch of ions from the 1,3 to the 2,4 configuration, and vice-versa. (From Morais-Cabral JH, Zhou Y, MacKinnon R. Energetic optimization of ion conduction rate by the K^+ selectivity filter. *Nature* 2001;414:37–42, with permission.)

Once cloned, the protein domains that participate in specific channel functions were identified by site-directed mutation, and a crude idea of the molecular architecture of ion channel pores emerged that was later seen in the solved structures for bacterial K^+ channels: hourglass in shape with a short tight selectivity filter (Figs. 6A and 6B). Na^+ and Ca^{2+} channels contain four homologous domains, each with six predicted membrane-spanning segments (Fig. 7A). Voltage-gated K^+ channel subunits are similar in size and topology to a single Na^+ channel domain (Fig. 7B). These channels share an overall tetrameric anatomy like that found for KcsA and other crystallized channels. A single conduction pore is formed either through pseudosymmetric folding of four homologous domains or aggregation of four independent subunits (45, 83). The residues linking every fifth and sixth membrane-spanning segment contribute to pore formation (P domains) and are arrayed centrally as four "pore loops" (84). Some K^+ channel subunits contain one P loop and two transmembrane segments, such as the KcsA channel (Fig. 7C); others have two P loops and four or more transmembrane stretches (Figs. 7D and 7E) (38).

The Pore

The first clue to the location of the pore came from studies of inhibition of the *Shaker* K^+ channel of *Drosophila melanogaster* by the scorpion neurotoxin charybdotoxin (81). Prior studies indicated that the toxin inhibited by physically binding in the ion conduction pathway and that binding involved negatively-charged channel sites (5, 80, 92). Systematic point mutation of negative channel residues revealed that a glutamate in the region linking transmembrane segments 5 and 6 (S5, S6) was a toxin interaction site and suggested the channel pore was nearby (81). Residues across this S5–S6 linker region were subsequently shown to be critical to toxin binding (39, 40, 79) and to contain sites mediating pore blockade by agents applied from both the extracellular and intracellular solution as expected if the residues span the membrane (82, 135). Comparison of sequences of cloned K^+ channels allowed identification of a "signature sequence" of eight highly conserved residues in the P domains of all K^+-selective ion channels (TMTTV-GYG in *Shaker* K^+ channels) (47, 48). These residues coordinate K^+ ions in the KcsA channel (Figs. 6A and 6B).

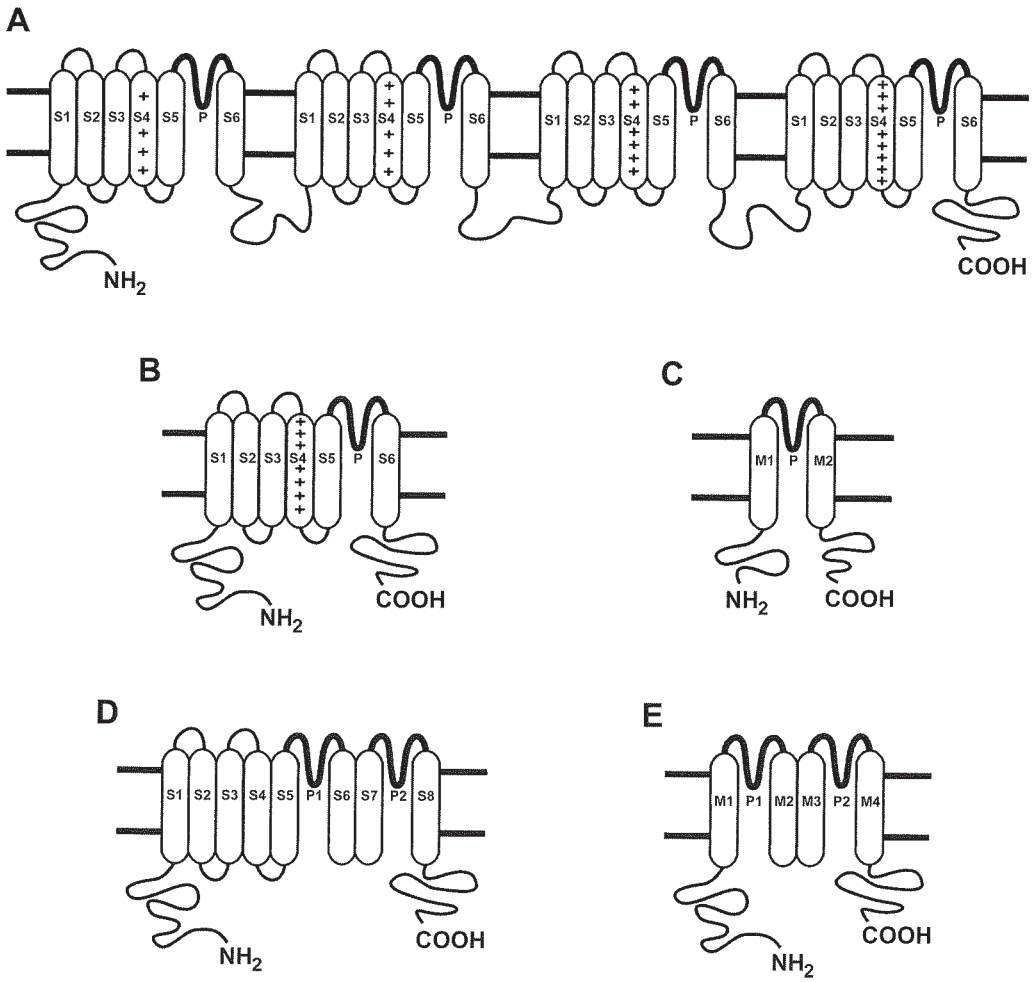

FIGURE 7 Probable membrane topologies of Na^+, Ca^{2+}, and K^+ channel pore-forming subunits. **A:** Voltage-gated Na^+ and Ca^{2+} channels. **B:** Voltage-gated K^+ channels. **C:** Inward rectifier K^+ channels, KcsA, and epithelial Na^+ channels. **D:** A two–P-domain outward rectifier K^+ channel. **E:** A two P-domain open rectifier K^+ channel.

The S4 Domain and Voltage Sensing

In 1952, Hodgkin and Huxley (53) first proposed that changes in voltage might cause movement of charged "gating particles" within nerve membranes to turn Na^+ and K^+ conductances on and off. After cloning revealed the primary sequences of the voltage-gated channels, residues in the fourth predicted transmembrane segment (S4) of each subunit or domain became the leading candidates for these voltage sensing charges (Figs. 7A and 7B) (100). S4 segments are marked by positively-charged arginine or lysine residues at every third or fourth position, a motif unique to voltage-sensing ion channels. Extensive evaluation of the effects of S4 mutagenesis on voltage-gated channel opening and direct evidence that the segment moves in response to changes in transmembrane voltage strongly supports the idea that S4 is a major part of the voltage sensor. Additionally, acidic countercharges are distributed in transmembrane stretches 2 and 3 of K^+ channels and these interact with the positive S4 charges to contribute to voltage sensing (10). The S4 segment appears to be at the periphery of the channel, with its charged residues facing centrally, based on studies of archaeal (25) and mammalian (75, 76) K^+ channels. At present, the movements of the voltage sensor are a topic of intense investigation.

Ligand Gating

Other channels are activated or closed by the binding of small molecules. Thus, two acetylcholine (ACh) molecules bind to the external face of the nicotinic ACh receptor channel of neuromuscular junctions leading to the opening of its cation-selective pore. In the heart, binding of ACh to muscarinic receptors liberates $G\beta\gamma$ in sinoatrial and atrioventricular nodal cells; the G-protein binds directly to cardiac K^+ channels leading to their activation. This explains the response of the heart to ACh released by the vagus nerve, which opens K^+ channels and allows an efflux of K^+ ions to shift the membrane to more negative potentials. This slows the heart rate by protracting the rise of membrane potential to the threshold for Na^+-channel activation (65). In neurons, there are myriad ligand-gated ion channels that respond to a variety of neurotransmitters to allow specific ion flux (i.e., a single ionic species) or nonselective cation or anion flux. Another mechanism by which ion channels can be modulated by ligand binding is via pore blockade. For example, intracellular Mg^{2+} and polyamines enter the pores of inwardly rectifying (IR) K^+ channels and physically interfere with ion permeation until the membrane voltage is negative to E_K and external K^+ ions can move into the pore to dislodge the blockers (77) (see discussion of cardiac action potentials in subsequent sections).

Activation and Inactivation Gates

The location and movement of the gates that close pores and move away during channel activation are not yet known for all ion channels. However, a comparison of structural data between KcsA and a bacterial calcium-gated K^+ channel (MthK) that was crystallized in the open configuration supports a mechanism by which the helices following the P domain form a gate by making an "inverted teepee" that blocks intracellular side of the selectivity filter (the inner vestibule). In the open state, these helices open the gate by bending at a glycine "hinge" to allow for ionic access to the pore (62). In other K^+ channels where this glycine residue is conserved, it is believed that this gating mechanism is also used. There is also experimental evidence to support a gate that blocks off the inner vestibule in voltage-gated K^+ channels (74). In K2P background channels, the activation gating appears to occur in the outer vestibule (142). Structural data from nicotinic ACh channels, suggests a third picture for channel opening: the binding of ligand to the extracellular region of the channel allows for conduction of cations by inducing a widening of the pore itself (126).

Fast inactivation of voltage-gated channels has been well delineated. Inactivation, as occurs in the Na^+ channels that initiate action potentials and many K^+ channels, is relatively voltage-insensitive and results from internal channel residues moving into the pore after the channel has opened (37, 57). It is by this mechanism that the regenerative activity of Na^+ channels is controlled (Fig. 4).

Modifying Channel Function

A Diversity of Channel Subunits

Most channels form by the association of multiple pore-forming subunits; this provides a mechanism for functional diversity: altered subunit composition (17). Thus, voltage-gated Cl^- channels are dimeric, ATP-gated 2PX receptor channels trimeric (or possibly hexameric, see [101]), voltage-gated K^+ channels tetrameric, and nicotinic acetylcholine receptor channels pentameric. Functional diversity can be generated by formation of heteromers of nonidentical channel subunits. For example, three of the four isoforms of G-protein–regulated inward-rectifier K^+ channels (GIRK2-4, or Kir3.2-3.4) can exist as homotetramers in the brain, but GIRK1 appears to complex with GIRK2 in mammalian cerebellar neurons. Also, GIRK1/4 heteromers underlie the I_{KACh} current of the heart (85). Similarly, the profile of K^+-channel currents from Kv1 (*Shaker*) family potassium channels in the brain is expanded by forming tetramers of one, two, or four different isoforms per tetramer (23).

Accessory Subunits

An even greater assortment of functional channels can be achieved by assembly of channel complexes with pore-forming and accessory subunits. All major classes of voltage-gated ion channels have been shown to stably interact with accessory subunits, which are often referred to as "β subunits." This growing list of accessory subunits includes soluble cytosolic proteins, type I and type II single transmembrane-spanning proteins, and subunits that span the membrane 2, 4, and even 17 times. Many of these proteins are depicted in Fig. 8.

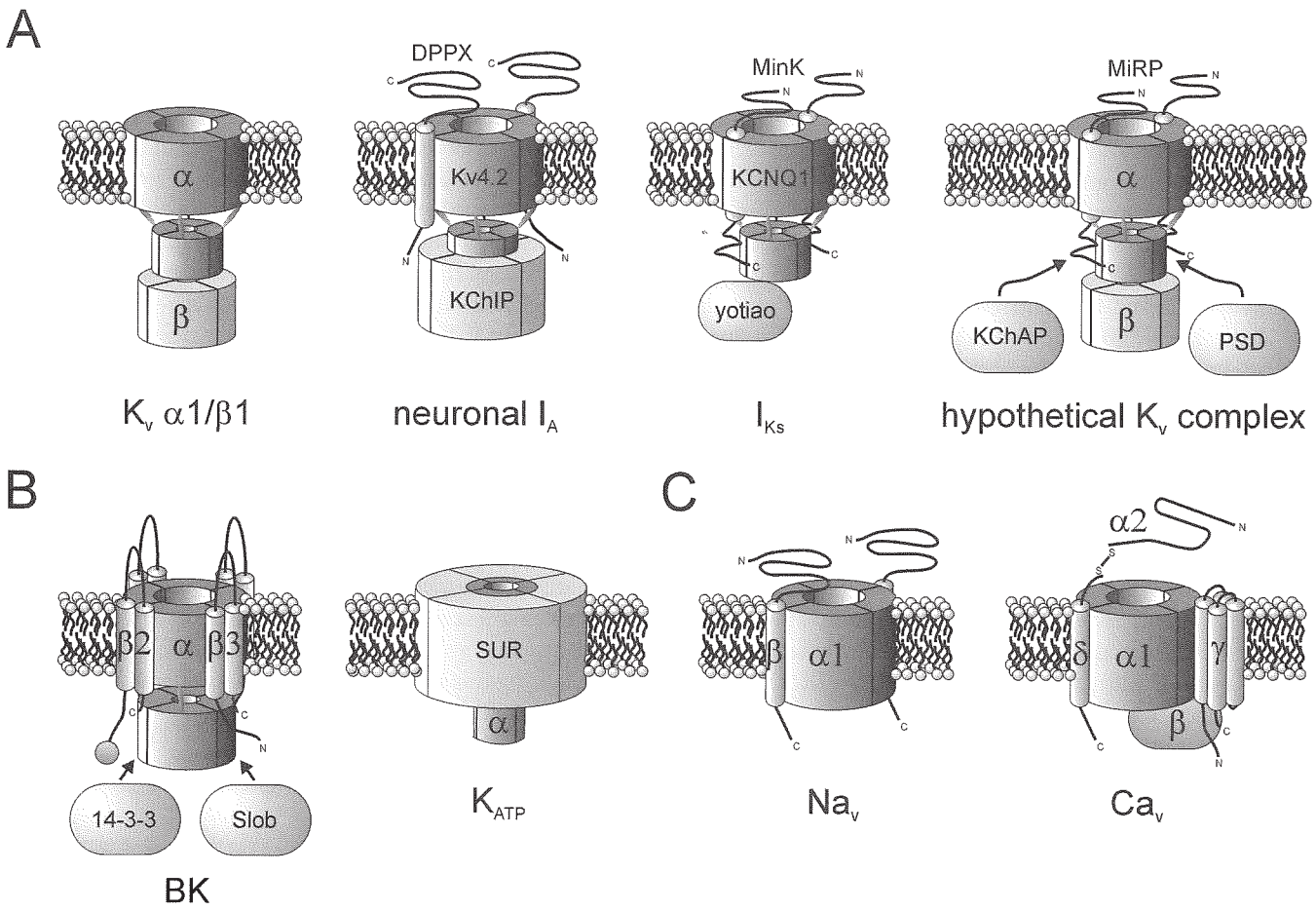

FIGURE 8 Some examples of ion channel accessory subunits. **A:** Cartoons representing K^+ channel complexes and native current correlate where known, showing pore-forming α and ancillary β subunits in relation to the plasma membrane. Left to right: A cytoplasmic β subunit ($K_v\beta1$) subunit tetramer docks tightly with the cytoplasmic N-terminal domains of an voltage-gated K^+ channel ($K_v\alpha1$) tetramer to form a $K_v\alpha1$-$K_v\beta1$ channel complex; four cytoplasmic K^+ channel interacting proteins (KChIPs) co-assemble with a Kv4.2 α-subunit tetramer and associated DPPX subunits, underlying the neuronal A-type (I_A) potassium current; a KCNQ1 α-subunit tetramer associated with 2 MinK subunits and the protein kinase A-protein phosphatase-1 targeting protein, yotiao, underlying the cardiac slowly activating delayed-rectifiers (I_{Ks}) potassium current; a hypothetical K_v channel complex comprising a tetramer of a subunits plus MinK-related peptides (MiRPs), K^+ channel associated protein (KChAP) and postsynaptic density protein (PSD). **B:** Ca^{2+} (BK) and ATP (K_{ATP}) sensitive K^+ channel complexes and their accessory subunits. BK channel α subunits can associate with transmembrane (TM) β subunits designated β1-4 and also interact with cytoplasmic Slob protein and the ubiquitous regulatory protein, 14-3-3. K_{ATP} channels co-assemble from four TM α subunits and four TM sulfonylurea receptors (SUR). **C:** Voltage-gated Na^+ (Na_v) and Ca^{2+} (Ca_v) channel complexes and their associated δ subunits. Na_v α subunits associate with TM β subunits; Ca_v channels comprise a complex assembly of a single TM β subunit linked by a disulfide bond to an extracellular α2 subunit, a four TM-domain γ subunit, and a cytoplasmic β subunit. (From McCrossan ZA, Abbott GW. The MinK-related peptides. *Neuropharmacology* 2004;47:787–821, with permission.)

One family of accessory subunits, MinK and the MinK-related peptides (MiRPs), are single transmembrane-spanning proteins that play a fundamental role in controlling K^+-channel gating kinetics, conductance, pharmacology, and trafficking (2, 87). The physiologic relevance of these proteins is exemplified by the association of clinical disorders with their mutation leading to congenital long QT syndrome, predisposition to drug-induced arrhythmia, sensorineural deafness, and periodic paralysis (1, 29, 114, 118). MinK, for example, endows the KCNQ1 channel with the unique biophysical properties—including slower activation and inactivation and a more depolarized threshold for activation—that allow it to operate the normal cardiac slow delayed rectifier current (I_{Ks}) (115, 118); and as a short-circuit K^+ conductance of proximal-tubule brush border that facilitates solute-coupled Na^+ transport (127). MiRP1 establishes the cardiac rapid delayed rectifier (I_{Kr}) current by assembly with the hERG K^+ channel (3) and may also complex with Kv4 and hyperpolarization-activated cation (HCN) channels in the heart that underlie the transient outward (I_{to}) (27, 139) and pacemaker (I_f) (26, 138) currents, respectively. In distinction to the effects of MinK on KCNQ1, the association of MiRP2 with KCNQ1 creates a noninactivating "leak" channel thought to function in the gastrointestinal tract (113). MiRP2 also partners with the predominate

skeletal muscle K^+ channel, Kv3.4, to lower the threshold for channel activation (1) and with Kv2.1 and Kv3.1 in brain to slow gating kinetics (88).

Another family of integral membrane proteins, KCNMB, has four family members, all of which alter the properties of the calcium- and voltage-gated K^+ channel, BK (also called MaxiK or K_{Ca}). BK is a widely expressed potassium channel that can attenuate Ca^{2+} influx from voltage-gated Ca^{2+} channels by hyperpolarizing the cell membrane in response to local elevations of Ca^{2+}. In vascular smooth muscle, BK channels co-associate with KCNMB1 (β1), which greatly increases their calcium sensitivity (89). This enables tight control of vascular tone in response to a rising $[Ca^{2+}]$, as demonstrated in a mouse model of hypertension, produced by a knockout of the *KCNMB1* gene (13). Rat adrenal chromaffin cells release catecholamines in response to electrical stimulation; a subset expressing KCNMB2 lack the ability to fire rapidly, while those expressing BK alone maintain a relatively hyperpolarized membrane potential to allow for repetitive firing (132). Splice variants of KCNMB3 expressed in spleen, liver, kidney, and pancreas endow BK with different degrees of inactivation (125), KCNMB4 is found predominately in the central nervous system, where it alters calcium-sensitivity and slows activation of BK (12).

To illustrate the rich variety of channel behaviors that can be produced by accessory subunits, consider the Kv4 family of voltage-gated K^+ channels that underlie rapidly activating and inactivating neuronal currents (A-type or I_{SA}) and more slowly inactivating, transient outward currents in the heart (I_{to}). In dog heart, expression of Kv4.3 mRNA is stable from the endocardium to the epicardium, even though I_{to} current amplitude is greater—and shows faster recovery from inactivation—in epicardial myocytes. The gradient of I_{to} parallels the expression of the soluble K^+-channel interacting protein 2 (KChIP2) that enhances surface expression and speeds recovery from inactivation of Kv4 channels (108). The surface expression, gating, and pharmacology of myocardial Kv4.3 can also be modulated by other soluble accessory proteins such as K^+-channel associated protein (KChAP) (67) and Kvβ (68, 133). In the brain, Kv4.3 channels interact in some cells with the integral membrane protein, dipeptidyl-aminopeptidase–like protein 6 (DPPX), leading to dramatically enhanced rates of activation, inactivation, and recovery from inactivation (99), whereas it associates in some interneurons with KChIP1 protein (105), These are examples of cellular "tuning" of the biophysical properties of one channel by accessory subunits to achieve different functions.

Posttranslational Modification

Ion channel properties can also be altered by posttranslational modifications such as glycosylation, palmitoylation, sumoylation, and partial proteolysis. The effects of N-linked glycosylation on channels are somewhat variable. For example, glycosylation can affect gating of Kv1.1 potassium channels (122) and Na^+ channels (140); whereas it increases surface expression/stability of the nicotinic ACh receptor (91), purinergic (P2X) receptors (124), and the hERG K^+ channel (42).

Palmitoylation involves a reversible attachment of the long-chain fatty-acid, palmitate, to modify protein–lipid interactions and target proteins to specific microdomains of the plasma membrane. The Kv1.1 potassium channel appears to be palmitoylated at the cytoplasmic linker between the S2 and S3 transmembrane segments to speed the channel's activation kinetics (44). The γ subunit of $GABA_A$ (γ-aminobutyric acid) receptor/channels are also palmitoylated, enabling clustering at the neuronal synapses (104).

Sumoylation involves the covalent modification with small ubiquitin-related modifier (SUMO) proteins that have generally been thought to mediate nuclear trafficking. However, sumoylation is now known to silence the background potassium channel, K2P1, of brain, heart, and kidney, while it resides in the plasma membrane (102). Another recently recognized modification is furin proteolysis of the α and γ subunits during maturation of the epithelial Na^+ channel, ENaC, which appears to be necessary for normal channel gating (59).

Second-Messenger Regulation

Like many other cellular proteins, ion channels are subject to regulation by a panoply of second messengers including kinases, phosphatases, nucleotides, phosphoinositides and other fatty acids, calcium ions, protons (pH), and reactive-oxygen species including nitric oxide. Consider again the calcium- and voltage-gated K^+ channel BK, which has multiple consensus sites for phosphorylation: BK channels may show increased or decreased activity when modulated by protein kinase A or protein kinase C, depending on the splice variant expressed. The channel can also be regulated by the cellular redox state, eicosanoids, nitric oxide, the heme molecule, and intracellular pH (121, 129). This is, of course, in addition to modulation of gating by cytosolic Ca^{2+}.

Drugs That Act on Ion Channels

Many drugs act on ion channels to modify their function. Some simply occlude the ion conduction pore while others alter channel activity by changing the opening or closing process. Lidocaine blocks Na^+ channels only when they are open. This is called use-dependent blockade. After application of the drug, the first depolarization elicits a nearly normal current indicating that little block has occurred; subsequent depolarizations show progressively smaller currents as the drug binds incrementally and does not unbind at rest (123). Conversely, the alkaloid batrachotoxin keeps Na^+ channels open on a time scale of hours while pinacidil, and diazepam, are examples of drugs that act to increase the open probability of ATP-sensitive K^+ channels and GABA-activated chloride channels, respectively. Since ion channels are in all cells, drugs can cause unintended side effects by action outside the target organ.

Indeed, most drugs act on more than one channel population. Quinidine blocks not only cardiac Na^+ channels but many K^+ channels and side effects are a major consideration when choosing antiarrhythmic therapies. Other drugs act to alter secondary messenger systems. In this way, epinephrine acts via G-protein–coupled receptors of the heart to increase cyclic adenosine monophosphate (cAMP) levels, protein kinase A activity, and phosphorylation of cardiac Ca^{2+} and K^+ channels, thus leading to increased activity of both channel types. The result is greater contractility (due to increased intracellular Ca^{2+}) and faster heart rate (due to increased K^+ flux and a shortened cardiac action potential).

EXCITABLE TISSUES

Impulse Propagation in Nerves

One of the key features of electrical signals is the speed at which they spread from one part of a cell to another (even in a long muscle fiber or nerve axon). Membrane potentials can extend passively by electrotonic spread; this mechanism is like the conduction of electricity through a wire. However, cells do not make good "wires" and conduction in this fashion has a limited range. Conversely, action potentials can spread without attenuation over long distances because of the regenerative action of voltage-gated ion channels. Both mechanisms operate in excitable cells.

Electrotonic spread is inefficient as membrane potential differences dissipate along the length of a cell because current flows not only axially within the cell but also escapes across its membrane through ion channels. How far an electrical signal can travel in this fashion depends on how much current flows in each pathway. The channels that establish the resting potential determine the membrane resistance (r_m) such that more open channels will reduce r_m, allowing more current to leak out of the cell and therefore dissipate a depolarized membrane potential. The length of propagation of an action potential is a function of the r_m and the axial resistance (r_{ax}, which is determined by the cross-sectional area and the resisitivity of the axonal cytoplasm) such that an increased r_m will allow for longer propagation but greater r_{ax} will reduce this distance. With about 10^5 open K^+ channels over a 1-cm length of a typical 10-μm nonmyelinated axon, the membrane resistance is about 100-fold smaller than the axial resistance, and most of the current will flow out of the membrane. Different strategies allow electrical signals to travel farther distances. These include increasing axon diameter (which will reduce r_{ax} by more than r_m) and by insulating regions of the axonal membrane with myelin to increase r_m.

Consider how action potential propagation occurs in a myelinated axon. In this case, Na^+ channels are restricted to nodes of Ranvier spaced roughly 1 mm apart. When a nodal membrane is depolarized by Na^+ entry the peak of the action potential is many times larger than threshold. This means that despite substantial attenuation of the signal due to the electrotonic decay (1/e, that is ~one third, of the signal remains for each millimeter traveled), an adjacent node will easily be brought above threshold, causing Na^+ channels in this node to open and the wave of depolarization to move along the fiber. Although the passive cable properties of the axon allow conduction of the depolarization to occur in both directions, the Na^+ channels of the recently depolarized nodes are inactivated and therefore regeneration and propagation of the action potential proceeds only in the forward direction.

Conduction in an unmyelinated fiber happens in the same general way except that Na^+ channels are distributed evenly along the cell and propagation occurs as a continuous process. Factors that affect conduction velocity include axon size (larger diameter axons have relatively less drop of the potential across the membrane), membrane capacitance (the capacitance per unit area of all cell membranes is essentially the same; however, a myelin sheath increases r_m, decreases capacitance and boosts conduction velocity 10- to 100-fold), Na^+ channel density (increased channel number decreases threshold and increases peak currents to increase conduction velocity) and Na^+ channel activity (diminished by drugs such as lidocaine and by temperature extremes, which slow opening or speed inactivation).

Electromechanical Coupling in Skeletal Muscle

When an action potential travels down a motor neuron from the spinal cord it reaches nerve terminals on a number of muscle fibers that compose its motor unit. The action potential depolarizes the presynaptic nerve terminal causing its voltage-sensitive Ca^{2+} channels to open. An influx of Ca^{2+} ions from the extracellular space leads synaptic vesicles to fuse with the cell membrane, releasing their stored ACh into the synaptic cleft (characteristically ~100 vesicles fuse, each containing ~1000 ACh molecules). The ACh molecules traverse the cleft and bind to ACh receptors (AChRs) on the muscle membrane (or sarcolemma) at localized regions, the motor end plates.

ACh binding causes AChRs to open and cations to flow; this depolarizes the muscle membrane, bringing its Na^+ channels to threshold and initiating an action potential. Continuous with the sarcolemma is a network of transverse tubules (T-tubules) that penetrate the entire cross-section of the muscle fiber. The function of the network is to propagate the action potential from the sarcolemma to the muscle center. The need for such a system is apparent if one considers the time course for most natural transduction processes that involve second messengers. Because muscle fibers are large (50–100 μm in diameter) diffusion of a soluble mediator from the surface membrane to the fiber center would take ~1 second. Electrical conduction transmits the stimulus to the contractile apparatus in milliseconds. Moreover, under normal conditions, the amount of ACh released is so

great that every nerve action potential results in a muscle action potential and contraction of the motor unit.

Signals from T-tubules are transmitted by a unique channel gating mechanism (Fig. 9). Action potentials travel from the sarcolemma to the T-tubular membrane where voltage-dependent L-type Ca^{2+} channels called dihydropyridine (DHP) receptors sense the depolarization. The signal then crosses to ryanodine receptors (also called Ca^{2+}-release channels) in the sarcoplasmic reticulum (SR); the SR is an intracellular membrane system that surrounds the muscles' contractile filament bundles called myofibrils. A high concentration of Ca^{2+} (~1 mM) is maintained inside the SR by an ATP-driven Ca^{2+} pump (the Ca^{2+}-ATPase) and it is Ca^{2+} release that allows muscle contraction; binding of Ca^{2+} to troponin shifts the position of tropomyosin on the actin filament, allowing myosin heads to interact with actin to generate force. The signal from the T-tubule travels through its DHP receptors by a direct mechanical linkage to the ryanodine receptors in the SR terminal cisternae to cause their opening and release of Ca^{2+} ions.

To control muscular movement, the termination of the response must also be rapid. This is achieved by three mechanisms. The primary event is re-uptake of Ca^{2+} into the SR. This is mediated by the Ca^{2+}-ATPase which is present at high density (>10,000 molecules/μm^2) and the Ca^{2+} buffering protein of the SR, calsequestrin, which can bind ~40 Ca^{2+} ions per molecule. Second, ACh in the synaptic cleft is rapidly hydrolyzed by acetylcholinesterase; it is choline that is taken back up into the nerve termini. Finally, repolarization of the T-tubule leads to closure of the ryanodine receptor halting release of Ca^{2+} from the SR. When no longer stimulated, the muscular action potential ends by the usual processes of Na^+ channel inactivation and opening of K^+ channels.

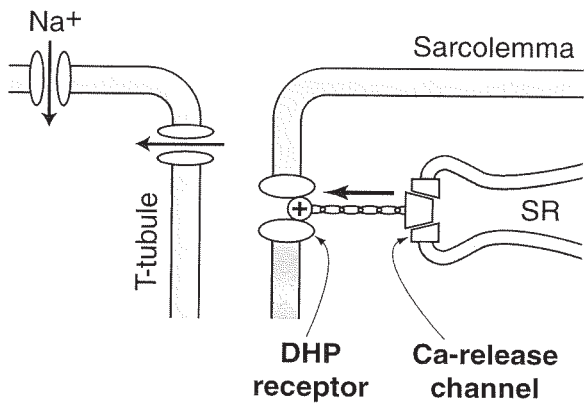

FIGURE 9 Schematic of skeletal muscle activation. Acetylcholine molecules bind to receptors in the motor end plates of the sarcolemma, causing these channels to open and initiating an action potential (Na^+ flux is indicated). This leads to depolarization of the T-tubule membrane network that penetrates the muscle fiber and contains voltage-gated Na^+ channels that propagate the signal rapidly and with high fidelity. Specialized junctions are present between T-tubules and the terminal cisternae of the sarcoplasmic reticulum (SR) called triads: In the T-tubule are dihydropyridine (DHP) receptors that sense depolarization and, apparently via a direct mechanical linkage, cause Ca^{2+}-release channels to open, leading to contraction. These Ca^{2+} channels (also known as ryanodine receptors) are large protein complexes formed by four 400-kD subunits that traverse the space between the T-tubule and SR membranes.

A single motor nerve axon may branch extensively and innervate many muscle fibers. Each muscle fiber, however, has only one endplate and therefore receives input from only one axon. The group of fibers innervated by a single neuron is called a motor unit. Weak contractions in a muscle group involve activity in small motor units with only a few fibers. To elicit larger forces, larger motor units are recruited. Thus, the small motor units in the extraocular muscles contain only three to six muscle fibers, whereas large motor units in the gastrocnemius can contain more than 1000.

Contraction can be blocked at each step by toxins and drugs. Thus, some Ca^{2+} channel blockers and botulinum toxin block release of ACh from nerve termini. Curare and snake toxins can block the ACh receptor. Most local anesthetics and tetrodotoxin block Na^+ channels. Dihydropyridines block the voltage-sensing action of the DHP receptor, whereas dantrolene blocks opening of the ryanodine receptor.

Smooth Muscle

Although smooth muscle controls the resistance of blood vessels, digestion of food, and uterine contraction (among many examples), it is much less well understood than skeletal or cardiac muscle. Like them, smooth muscles contract due to actin-myosin interactions; however, control of contraction and the geometry of smooth muscle filaments are unique. Smooth muscles are sensitive to a wide variety of mediators including hormones, peptides, and diffusible messengers like nitric oxide (NO). Thus, vascular smooth muscles relax in response to ACh, epinephrine, NO, atrial natriuretic peptide, and prostaglandin I; they contract to norepinephrine, angiotensin II, and in response to mechanical stretch.

Smooth muscle cells are smaller (2–10 μm in diameter, 100–500 μm in length) than skeletal muscle fibers and have no T-tubules. They do have a small SR compartment that stores Ca^{2+} ions. Although Ca^{2+} activates contraction in smooth muscle cells, it is by a different mechanism than in skeletal muscle. Here, the primary control of contraction is phosphorylation of myosin, which allows it to interact with actin. The phosphorylation is catalyzed by the myosin light-chain kinase, an enzyme activated by Ca^{2+} through the binding of a Ca^{2+}-calmodulin complex. Smooth muscle cells are sometimes electrically coupled to allow waves of electrical activity as seen in the gastrointestinal tract or uterus.

Some interesting types of channels observed in smooth muscle include BK channels, which are opened by depolarization and/or rises in intracellular Ca^{2+}; stretch-activated cation channels; receptor-operated Ca^{2+} channels that do not require membrane depolarization to activate; and ATP-sensitive K^+ channels that are normally held closed by the

presence of intracellular ATP and function primarily under ischemic conditions when ATP levels fall.

Cardiac Action Potentials

Unlike skeletal muscle, the heart beats by itself. Innervation of the heart by the autonomic nervous system serves to modulate the rate and strength of contractions. Pacemaking in the heart is provided by specialized myocardial nodal cells that produce rhythmic action potentials. The timing of action potential propagation in the heart from sinus node to Purkinje fiber to working muscle is uniquely important for its effective function as a pump. Although cardiac myocytes are striated muscle cells, they differ from skeletal myocytes in that calcium influx from L-type Ca^{2+} channels (DHP receptors) play a much greater role in triggering Ca^{2+} release from the ryanodine receptors (so-called "Ca^{2+}-induced Ca^{2+} release").

The action potential in working muscle and Purkinje fibers is similar to that in axons, in that voltage-gated Na^+ and K^+ channels play a central role. These cells exhibit a pattern of cyclical excitability with five phases (Fig. 4). Phase 0 is an explosive rise in membrane potential due to a rush of Na^+ into the cell (down its concentration gradient) through voltage-gated Na^+ channels that open with membrane depolarization; these channels then rapidly inactivate. Phase 1 is a brief repolarization step mediated by voltage-gated K^+ channels that open with depolarization and, like phase 0 Na^+ channels, rapidly inactivate. Because outward flow of K^+ (down its concentration gradient) makes the cell interior more negative, opening K^+ channels shifts the cell toward more negative potentials. Phase 2, the plateau in the action potential, is coincident with myocardial contraction and results from the cumulative activity of a number of channel and carrier-type transporters. The duration of phase 2 is determined by the activity of voltage-gated Ca^{2+} channels, as well as K^+ channels that open with a delay in response to membrane depolarization and remain open until the membrane is again hyperpolarized. These delayed outward K^+ currents return the membrane to its resting potential during phase 3 and allow the heart to relax. Phase 4, the pacemaker potential, is a slow rise in membrane potential attributed to closing of other K^+ channels and the slow opening of hyperpolarization-activated cation channels and instigates the next cycle of excitation and contraction. In broad outline, cardiac excitation results from rapid, voltage-dependent gating of Na^+ channels; delayed, voltage-dependent gating of K^+ channels; and the ability of both channel types to discriminate between Na^+ and K^+ ions.

The heart differs from other excitable tissues in having a longer action potential duration (APD) and a longer refractory period that lasts several hundred milliseconds. During the refractory period, the muscle is unresponsive to electrical stimuli and will not conduct action potentials. The long duration of cardiac action potentials is largely due to the action of Ca^{2+} channels. Ca^{2+} channels are much like Na^+ channels: They are activated by depolarization and they inactivate. However, both processes are much slower in Ca^{2+} channels, so that if subjected to a long depolarization, Ca^{2+} currents are maintained. This allows the membrane to sustain its depolarized status during plateau. Moreover, these channels are essential for Ca^{2+} entry into the myocardial cells to produce contraction. Thus, Ca^{2+} channel blockers decrease the height and duration of the cardiac action potential as well as the force of contraction. These differences between Ca^{2+} and Na^+ channels explain the behavior of pacemaking tissue of the heart (sinoatrial and atrioventricular nodes) when compared with the conduction system (His bundle and Purkinje fibers) and working myocardium. Na^+ channels support rapid conduction in the His-Purkinje system and working muscle, but are inactive in nodal tissue. Ca^{2+} channels generate the slow upstroke characteristic of nodal cells and are responsible for supporting a prolonged plateau phase in the His-Purkinje system and working muscle.

The resting potential of cardiac muscle cells is quite negative. This suggests that a powerful K^+ current is active at rest. These currents are mediated by inward rectifier (IR) K^+ channels, which open when the membrane is hyperpolarized below E_K but close above this potential. The IR channels hold the potential near E_K, but do not interfere with action potential development because they do not pass current at the depolarized voltages where Ca^{2+} or Na^+ channels initiate the upstroke. A rectifier is an electronic device that allows current to pass only in one direction. Analogously, the IR channels cannot pass K^+ ions when current flow becomes outward. The mechanism underlying this behavior is remarkably simple (Fig. 10). At potentials positive to E_K, the outflow of ions is impeded because intracellular Mg^{2+} and polyamines are driven into the pore and physically occlude the conduction pathway. At potentials more negative than E_K, K^+ ions entering the pore from the outside electrostatically "knock" the blocking ions out of the pore to open it for inward ion flux. This mechanism can explain a paradoxical result that can be found in cells that greatly depend on IR channels to maintain the resting membrane potential: although the Nernst relation (Eq. 1) would predict that lowering serum K^+ should make cells more negative by lowering E_K, fewer K^+ ions outside will allow IR channels to remain blocked, and the membrane potential can become more positive as other ionic conductances become predominant.

Pacemaking nodal cells of the heart have relatively few IR K^+ channels to keep resting membrane potential near E_K and express a nonselective cation current (I_f) that activates during the hyperpolarized phase 4 of the cardiac cycle to cause a progressive depolarization. As a result, resting membrane potential is more positive and voltage-gated Na^+ channels are largely inactivated, whereas voltage-gated Ca^{2+} channels remain able to open. These slowly activating Ca^{2+} channels produce the shallow phase 0 upstroke characteristic of cardiac nodal pacemaking cells.

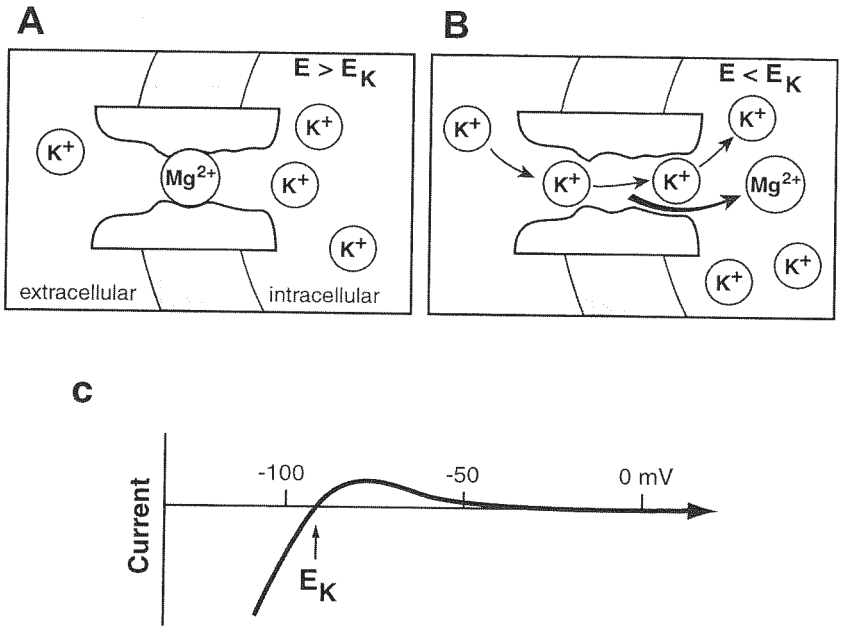

FIGURE 10 Inward rectifier K^+ channels are active near resting membrane potential. A rectifier is a device that allows current to pass in only one direction; inward rectifier K^+ channels allow inward currents but shut down as flux becomes outward. The mechanism is elegantly simple: at potentials positive to the Nernst equilibrium for K^+ ($E > E_K$), the outward flow of ions allows blocking ions (cytoplasmic Mg^{2+} and polyamines) to be driven into the pore where they bind with high affinity and block ion flow (**A**). At potentials that are negative to E_K ($E < E_K$), K^+ ions entering from the outside sweep the blocking ions out of the pore and keep it open for K^+ influx (**B**). The potassium current through these channels is shown in **C**, emphasizing why these channels are called inward rectifiers.

DISORDERED EXCITABILITY

Diseases of Ion Channels

As the molecular basis for ion channel function has been revealed, so has the basis for an increasing number of ion channel-mediated diseases. Because of the critical participation of ion channels in cellular physiology, diseases of these channels affect not only excitable cells but also nonexcitable tissue such as lung, bone, pancreas, and of course, the kidney. "Channelopathies" may represent either inherited or acquired loss or gain of channel function and have provided physiologists with a great deal of insight into normal physiology, ion-channel structure and function, mechanisms of inter- and intracellular signaling, and the bases of bulk electrolyte transport. Well over 50 channelopathies have been described and many are reviewed by Hübner and Jentsch (58). In addition, channelopathies of renal salt transport are discussed in Chapter 36.

Mutations that lead to loss of function can be due to low levels of channel protein in the membrane. Thus, the most common variant of cystic fibrosis is marked by inherent instability of the CFTRΔ508 Cl^- channel protein leading to its rapid intracellular degradation. Mutation of barttin, an accessory subunit involved in the normal surface expression of CLC chloride channels in the inner ear and in the nephron's thick ascending limb, can cause salt wasting and deafness (Bartter syndrome type IV) (31,32). Autoantibodies mediate channel degradation in myasthenia gravis, Lambert-Eaton syndrome and one form of acquired myotonia. Alternatively, loss-of-function disorders can be seen when channels reach the membrane and have a normal turn-over rate but show decreased activity. Examples in humans include persistent hyperinsulinemic hypoglycemia of infancy (PHHI) and the inherited congenital myotonias (Thomsen and Becker syndromes) in which channels open poorly or stay open for only a short time. Other loss-of-function disorders are the result of decreased single-channel conductance, inappropriate down-regulation, decreased agonist affinity, and blockade by drugs or poisons.

Disorders resulting from gain of function include hyperkalemic periodic paralysis (HYPP) in which channels open too readily and paramyotonia congenita (PC) in which they inactivate too slowly. Liddle syndrome is effectively a disorder of apparent mineralocorticoid excess that is largely mediated by reduced turnover at the cell surface of mutant epithelial Na^+ channel (ENaC) subunits. Other gain-of-function diseases are due to channels that have an abnormally high open probability due to mutations or exogenous activation by drugs or poisons. The pathophysiology of neuronal cell death in stroke appears to involve dysfunctional up-regulation of *N*-methyl-D-aspartate (NMDA) receptors (glutamate-activated Na^+ and Ca^{2+} channels).

In addition to rare diseases, there are common polymorphisms of ion channels that can predispose individuals to disease, such as a variant ENaC subunit that is associated with sodium-sensitive hypertension (7) or the T8A polymorphism of MiRP1 (KCNE2) that increases susceptibility to sulfamethoxazole-related long QT syndrome (114).

Electrolyte and pH Abnormalities

The central role of K^+ in setting cellular resting potential explains why abnormal serum K^+ levels produce the most common and prominent signs and symptoms referable to altered excitability. Abnormalities of calcium, magnesium, and pH can also affect neuromuscular excitability and cardiac pacemaking; and such manifestations will be exacerbated by potassium disturbances. Whereas hypo- and hypernatremia can disturb neurologic function, this is largely the result of movement of water with subsequent altered intracranial pressure (6). The clinical manifestations and management of these electrolyte disorders are discussed in greater detail elsewhere in this text; here, we consider the situations in which altered ionic and acid-base composition produce electrophysiologic effects. Each can be understood in terms of the basic concepts we have presented.

Potassium

Rate of change of Kext and symptoms: As described previously, it is the ratio of K^+ concentration in the intracellular and extracellular fluids that determines membrane excitability. Since K^+ is primarily restricted to the intracellular fluid, the ratio K_{in}/K_{ext} is influenced predominantly by the relatively small K^+ concentration in the extracellular compartment. As a result, minor shifts of K^+ into or out of cells can produce large and potentially lethal changes in K_{ext}. One can generalize that changes in K_{ext} will produce effects by altering resting membrane potential; that hypokalemia tends to produce hyperpolarization; and, conversely, that hyperkalemia leads to depolarization. However, the effects of altered K^+ also depend on the speed at which K^+ levels change. Thus, acute hypokalemia, as seen in severe diarrhea, leads a greater decrease in extracellular than intracellular K^+ levels. From the Nernst relation (Eq. 1) we calculate that E_K under normal ionic conditions (155 K_{in}, 4.0 K_{ext}) is -97 mV while it is -114 mV in acute hypokalemia (145 K_{in}, 2.0 K_{ext}). Hyperpolarization moves the membrane potential away from threshold leading to decreased excitability and symptoms of weakness or paralysis. With a slower depletion of body potassium stores, intracellular K^+ of skeletal muscle can fall as much as 30% (119), shifting E_K to only -107mV (112 K_{in}, 2.0 K_{ext}), minimizing symptoms. Similarly, hyperkalemia that develops rapidly, as seen in tumor lysis syndrome, can shift E_K to -68 mV (160 K_{in}, 12.5 K_{ext}) producing paralysis and arrhythmias secondary to Na^+-channel inactivation and conduction failure. Conversely, chronic hyperkalemia with compensation is more likely to produce partial depolarization (170 K_{in}, 8 K_{ext}, $E_K = -82$ mV) (106) and a lower risk for adverse sequelae.

Hyperkalemia: a medical emergency: Hyperkalemia rarely elicits extracardiac manifestations until serum levels rise above 8.0 mEq/L, at which point an ascending muscular weakness may occur that can progress to a flaccid paralysis (130) or diaphragmatic paresis (36). The initial—and most worrisome—toxic effects of hyperkalemia are cardiac and include complete heart block, ventricular fibrillation, and cardiac arrest. In the heart, elevated extracellular K^+ tends to depolarize excitable cells and lead to Na^+ channel inactivation. This produces an attenuated ventricular action potential upstroke (now carried largely by inward Ca^{2+} currents) and slowed propagation of excitation across the myocardium (Fig. 11). An additional effect of the high K_{ext} is increased amplitude of the delayed rectifier K^+ current, apparently effected by enhanced recovery from inactivation of I_{Kr} (11, 134). The increased K^+ current steepens the slope of phase 3 of the cardiac action potential, thereby speeding myocardial repolarization. The ECG with hyperkalemia is notable for a dampening of P waves (due to pronounced attenuation of the action potential in atrial cells), T waves that are large and peaked (due to accelerated repolarization), and— with severe hyperkalemia—a widening of the QRS complex (due to slow propagation of excitation) (120).

These ECG changes signify a profound derangement of the myocardial conductances, explaining why this scenario can rapidly degenerate to ventricular fibrillation. Potassium intoxication occurs with renal failure, hemolysis, tissue necrosis, adrenal failure, drugs that interfere with K^+ excretion, and excessive K^+ supplementation. Hypocalcemia, hyponatremia, and acidosis all exacerbate the effects of hyperkalemia.

Hyperkalemia is a genuine electrolyte emergency. Current recommendations include urgent care for any patient with evidence of hyperkalemia on a surface electrocardiogram or serum levels above 6 or 6.5 mEq/L. Treatments are aimed toward antagonizing the effects of hyperkalemia on membrane potential, rapidly lowering serum K^+ by shifting it from the extracellular compartment into cells, and removing K^+ from the body. Treating the disorder that led to hyperkalemia and minimizing other factors that increase K_{ext} are also appropriate. Specific measures include the administration of intravenous calcium, which can reverse electrocardiogram changes in minutes by directly antagonizing the effects of hyperkalemia on membrane potential (see following section on calcium). Shifting K_{ext} into cells is favored by administration of insulin (along with glucose, to prevent hypoglycemia). If the patient is acidemic, sodium bicarbonate is also effective. Finally, inhalation of 10 to 20 mg of the β_2-selective catecholamine albuterol is to be considered (4, 73), as stimulation of the β_2 receptors can activate the Na^+,K^+-ATPase via cAMP to move K^+ into cells (15, 20). Insulin might similarly stimulate the Na^+, K^+-ATPase (22), or perhaps the ATPase is secondarily activated by a rise of intracellular Na^+ caused by activation of Na^+-H^+ countertransport (110). If a metabolic acidosis

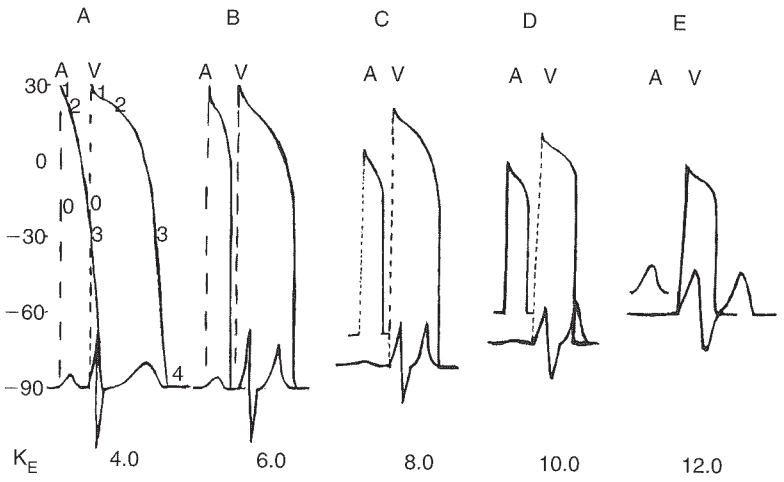

FIGURE 11 Electrophysiologic recordings of atrial (A) and ventricular (V) action potentials (AP) from isolated rabbit hearts, superimposed on the electrocardiogram. The y-axis shows the transmembrane potential in millivolts; and the extracellular K^+ (K_E, in mEq/L) concentration is noted below each set of tracings. In tracings **A** and **B**, the resting membrane potential (RMP) is −90 mV and the total amplitude of the AP is 120 mV. Note how increasing K_{ext} leads to a rise of the RMP and a reduced amplitude of the AP; with a greater effect seen in the atrium. Also note the shorter duration of the AP, and the significantly accelerated phase 3 hyperpolarization. The slope of phase 3 correlates with the downslope of the T-wave on the electrocardogram, causing a "peaking" effect. (From Surawicz B. Relationship between electrocardiogram and electrolytes. *Am Heart J* 1967;73:814–834, with permission.)

exists, then administration of bicarbonate will buffer serum protons and promote Na^+-H^+ exchange, and subsequently activate Na^+,K^+-ATPase activity (46). Removing K^+ from the body is achieved with the use of diuretics or oral/rectal administration of cation exchange resin. Often critical in those with significant renal impairment, hemodialysis can lower K_{ext} much more rapidly. It should be noted that digoxin therapy and left ventricular hypertrophy are risk factors for complex ventricular arrhythmias when dialysate K^+ is as low as 2.0 mEq/L (97).

High external K^+ levels seen in healthy subjects during exercise are not associated with arrhythmia. Elevated levels of circulating catecholamines appear to be an important protective factor as they increase Ca^{2+} currents and counteract the effects of hyperkalemia. Catechols increase the upstroke and duration of cardiac action potentials and decrease the tendency toward arrhythmia associated with slow impulse propagation and shortened refractory period.

Hypokalemia: Hypokalemia produces a variety of clinical disturbances including drowsiness, fatigue, anorexia, constipation, weakness, and flaccid paralysis. At extremely low levels (< 1.5 mEq/L), muscle necrosis can occur as well as ascending paralysis with eventual impairment of respiratory function (130). The electrocardiogram is notable for long QT intervals and flattened T waves. Since ventricular action potentials lengthen more than those in the atria, atrioventricular block can develop. Cardiac rhythm disturbances are rare in patients without underlying disease. However, those taking digoxin and those with cardiac ischemia, heart failure, or left-ventricular hypertrophy are at risk for development of arrhythmias even with mild to moderate hypokalemia (86). This may be partly mediated by a downregulation of cardiac potassium channels with these conditions (98). In addition, other causes for prolonged QT interval, including medications or congenital and acquired channelopathies, will also increase the risk of hypokalemia-associated arrhythmia (107).

Hypokalemia is most often the result of K^+ depletion due to abnormal losses but rarely is due to abrupt shifts from the extracellular to intracellular compartment. K^+ loss through the kidney secondary to chronic use of diuretics or in the stool as a result of diarrhea are most common. Some other causes of hypokalemia include renal tubular defects, starvation, vomiting, diabetic ketoacidosis, and hyperaldosteronism.

A rare cause of hypokalemia is intoxication with barium salts, which indirectly causes a profound shift of serum K^+ into cells. Barium effectively blocks background ("leak") potassium channels, but does not alter Na^+,K^+-ATPase activity (21, 116). Thus, K^+ is pumped into cells but does not leak out; the intracellular accumulation of K^+ can lead to a life-threatening hypokalemia (72).

Potassium depletion will increase systolic and diastolic blood pressure when sodium intake is not restricted (24, 66) and potassium supplementation can have a mild salutary effect on systemic blood pressure (131); although low serum K^+ levels do not clearly correlate the development of hypertension in the general population (128). In addition, potassium supplementation may reduce the risk of stroke in some populations (33, 43, 117). The hypertensive effect of hypokalemia may be due to increased contraction of vascular smooth muscle by reduced activity of Na^+,K^+-ATPase,

raising Na^+_{in} and causing cellular depolarization. The increased Na^+_{in} will inhibit Na^+/Ca^{2+} exchange and also promote smooth-muscle contraction by raising Ca^{2+}_{in} (19). In addition hypokalemia may also promote cardiovascular disease by stimulating smooth-muscle proliferation and platelet aggregation (137).

Calcium

Hypocalcemia: Approximately 45% of serum Ca^{2+} is bound to protein, primarily albumin. Bound Ca^{2+} is in equilibrium with the soluble ionized fraction that influences membrane excitation. The most common cause of reduced total serum Ca^{2+} is hypoalbuminemia, however, ionized Ca^{2+} is normal in this condition. The ratio of bound and free Ca^{2+} is altered by acid-base status and this can influence excitation: acidosis increases the ionized fraction while alkalosis decreases it. Common causes of true hypocalcemia include vitamin D deficiency, acute pancreatitis, magnesium deficiency, hypophosphatemia, hypoparathyroidism, pseudohypoparathyroidism, and renal tubular acidosis. Common symptoms are tetany, confusion, and seizures. Hyperkalemia and hypomagnesemia potentiate the cardiac and neuromuscular irritability produced by hypocalcemia, and vice versa.

Hypercalcemia and membrane stabilization: Hypercalcemia is caused by hyperparathyroidism, neoplastic disorders, vitamin D intoxication, sarcoidosis and other pulmonary granulomatous diseases, milk-alkali syndrome, immobilization, hyperthyroidism, and acute adrenal insufficiency. Symptoms include nausea, vomiting, constipation, polyuria, psychosis, and coma. Serious arrhythmias from hypercalcemia are relatively rare, although the length of the QT interval is inversely proportional to the serum Ca^{2+} concentration.

Increased extracellular Ca^{2+} is said to stabilize excitable cells, rendering them less responsive; low pH has the same effect. At first, this effect appears to be paradoxical. Inward Ca^{2+} currents are associated with excitation and are, in fact, seen to increase when external Ca^{2+} concentration is elevated. The stabilization is instead due to the strong effect of Ca^{2+} on the voltage sensitivity of voltage-gated channels, especially Na^+ channels. Membrane proteins can have fixed negative charges near their extracellular surfaces, contributed by polar amino acids and/or carbohydrates. These sites will preferentially bind divalent cations in the extracellular milieu. Channels in the membrane experience not only to the potential difference across the membrane (E_m) but also from these charges, and they respond to a local potential difference across the interior of the membrane (ψ). While ψ_i follows E_m, the channel senses the more positive local potential ψ_i. Thus, at -50 mV, where Na^+ channels begin to activate, ψ_i is close to 0 mV. As external Ca^{2+} is raised it binds with fairly high affinity to the local binding sites. As a result, ψ_i is no longer so positive, and from the point of view of the Na^+ channel the local environment is more hyperpolarized. Thus, it takes a greater depolarization to achieve activation threshold. Hydrogen ions have the same effect: titrating acidic groups on the surface neutralizes negative surface charges and moves Na^+ channels away from their threshold for activation. This simplified explanation is more fully discussed in Chapter 20 of (51).

Magnesium

Critical to a variety of cellular functions, especially those that use ATP, disturbances in magnesium can affect many organs including the heart and neuromuscular system. Magnesium balance depends on intake and renal excretion which is regulated in the distal nephron. Depletion of body Mg^{2+} may be caused by renal tubular wasting from congenital disorders or agents such as diuretics or nephrotoxins, or may follow reduced intake from malnutrition or enteropathies. Negative balance results in decreased serum and intracellular levels, while renal failure may allow for rapid elevation of serum Mg^{2+} As discussed in Chapter 61, hypomagnesemia can cause neuromuscular irritability and increase the risk of cardiac arrhythmia. In some respects, Mg^{2+} and Ca^{2+} have similar mechanisms of action in that reduced extracellular concentrations will effectively lower the threshold for action potentials (49) (see previous discussion of hypercalcemia). While these divalents may share some extracellular binding sites, the fact that isolated hypomagnesemia or isolated hypocalcemia can promote neuronal excitability suggests that there are also sites that selectively bind one cation over the other.

With respect to cardiac excitability, hypomagnesemia (like hypocalcemia) acts to exacerbate hypokalemic and digitalis toxicity and increase the risk for ventricular arrhythmia. This may be partly related to surface-potential effects, but low Mg^{2+}_{ext} also enhances activation of hERG (I_{Kr}) (52), leading to abnormally fast repolarization. Further, a reduction of intracellular Mg^{2+} concentration can increase outward K^+ currents from IR channels, hyperpolarizing cardiomyocytes (Fig. 10). Because potassium-sparing diuretics minimize Mg^{2+} depletion, they should be considered in patients at high risk for arrhythmia (56).

In vascular smooth muscle, Ca^{2+} and Mg^{2+} have antagonistic effects, such that hypomagnesemia actually promotes smooth-muscle contractility. This appears to be related to lowered intracellular Mg^{2+}, as Mg^{2+} acts as an inhibitor of IP_3-mediated (70) and calcium-mediated (71, 90) Ca^{2+} release from the sarcoplasmic reticulum. In contrast to smooth muscle, cardiac myocytes respond to hypomagnesemia with a slight decrease of contractility (69, 103); although the mechanism of this phenomenon is less well understood. Taken together, this explains improved blood pressure with moderate Mg^{2+} levels due to improved cardiac contractility (69, 103), and vasodilatation-associated hypotension seen with boluses of Mg^{2+} salts for treatment of preterm labor.

Acid-Base Status and Excitability

Each of the four primary acid-base disturbances (as well as mixed disorders) gives rise to secondary compensatory responses. Thus, respiratory acidosis induces a secondary increase in HCO_3^- to return blood pH toward normal. In general, acidemia (increased extracellular H^+) will inhibit

Na^+-H^+ countertransport, leading to reduced intracellular Na^+ and therefore increased extracellular K^+. This can lead to hyperkalemia with its attendant cardiovascular risks. Conversely, alkalemia (decreased extracellular H^+) leads to increased inward K^+ and Na^+ flux and may produce hypokalemia. Serum Na^+ is rarely altered significantly by changes in pH due to its normally high serum level.

There are also specific effects of protons on ion channels. For example, H^+ ions can bind to negative charges on the external face of Na^+ channels, to shift the surface potential in the same fashion as Ca^{2+} or Mg^{2+} ions (50 and therefore reduce Na^+-channel activity. However, there seems to be a converse effect on cardiac pacemaker channels (14), so that acidemia can actually potentiate cardiac irritability.

The Big Picture: Response to Electrolyte Disorders Has Many Mitigating Factors

Based on our understanding of the many factors involved in membrane excitability, we can begin to understand why one patient may transiently tolerate a serum K^+ level of 8.0 mEq/L and another may suffer sudden death related to a K^+ of 7.0 mEq/L. The response of excitable tissue will be dependent upon the chronicity of the hyperkalemia (affecting intracellular levels, and therefore membrane potential); the state of the autonomic nervous system, affecting levels of ACh and catecholamines on the heart; the presence of any drugs that can alter intracellular calcium concentration or cardiac ion channel activity; levels of other electrolytes or protons in the serum; and genetic polymorphisms in ion channel pore-forming and accessory subunits and other proteins. Further, it seems reasonable to speculate that derangements of electrolytes may lead to compensatory second-messenger modulation of ion channels or altered expression of ion channels and/or their accessory subunits, as demonstrated in failing hearts (61, 78, 98, 111)

SUMMARY

Ion channels mediate the electrical activity of all cells. Their function in excitable tissues like nerves and muscles is particularly relevant to clinical medicine. These proteins are characterized by their finely timed opening and closing, high throughput, and high selectivity. Ion channels form transmembrane water-filled pores with multiple ion binding sites in tandem. Disorders of electrolytes affect cellular function through altered excitability. Numerous common medications and several ion-channel polymorphisms influence ion channel activity and may exacerbate the effects of electrolyte disorders on the function of nerve, muscle, and heart. The mechanism underlying most channel-mediated disorders is yet to be discerned, and some diseases have yet to be recognized as due to ion-channel dysfunction. However, rapid progress has been made over the last 15 years, enhancing our understanding of basic mechanisms and our capacity to treat disorders of membrane excitability.

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